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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/656,531

09/05/2003

David Baltimore

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EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

11/14/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/656,531

Applicant(s)

BALTIMORE ET AL.

Examiner

DELIA M. RAMIREZ

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**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period **will** apply and **will** expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply **will**, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 21,28,40,43,99-104,107-113,120-135 and 137-143 is/are pending in the application.
- 4a) Of the above claim(s) 43,109-113,120-135 and 137-143 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21,28,40,99-104,107 and 108 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

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## **DETAILED ACTION**

### ***Status of the Application***

Claims 21, 28, 40, 43, 99-104, 107-113 and 120-135, 137-143 are pending.

Applicant's amendment of claims 21, 28, 40, 43, 127, and cancellation of claims 106, 119, 136, as submitted in a communication filed on 8/6/2008 is acknowledged.

At this time, no product claim is found allowable. Therefore the restriction requirement between product and process claims can be properly maintained.

Claims 43, 109-113, 120-135, 137-143 are withdrawn from consideration as being directed to a non-elected invention. Claims 21, 28, 40, 99-104 and 107-108 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112, First Paragraph***

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 21, 28, 40, 99-104 and 107-108 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the previous Office action mailed on 5/13/2008.
3. Applicant argues that the skilled artisan knew that Zinc finger DNA binding domains were structurally related and that the state of the art teaches that these structurally related domains can be modified in their recognition helices so as to recognize any selected target site. Applicant refers to known methods for designing chimeric nucleases with varied DNA recognition sequences such as using

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polypeptide display libraries in an affinity selection step to select variant fingers that bind to the target site.

4. Applicant's arguments have been fully considered. In view of applicant's amendment which now limit the genus of DNA binding domains to zinc finger DNA binding domains, and in view of the teachings of the art regarding (1) which structural features are conserved in zinc finger DNA binding domains and which structural features can be modified to obtain specificity to a particular target, and (2) methods known in the art, such as polypeptide display libraries, to select variant fingers which would bind to the desired target (U.S. Patent No. 6140466, 6007988, 6645342, 6013453, Wolfe et al., Annu Rev Biophys Biomol Struct, 3:183-212, 1999 (IDS)), this rejection is hereby withdrawn.

5. Claims 28, 40, 103, 107, 108 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mammalian cell that comprises (a) a vector containing a nucleic acid encoding a chimeric nuclease, wherein said chimeric nuclease comprises a Zinc finger DNA binding domain that recognizes 5' GGGGAAGAA 3' or 5' GCGTGGGCG 3', or (b) the chimeric nuclease encoded by the vector of (a), does not reasonably provide enablement for a **non-isolated** mammalian cell comprising (i) a vector having a DNA encoding a chimeric nuclease, wherein said chimeric nuclease comprises a zinc finger DNA binding domain and a cleavage domain, and a DNA encoding a repair substrate, or (ii) the chimeric nuclease encoded by the vector of (i). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

6. This rejection has been discussed at length in the previous Office action mailed on 5/13/2008. It is maintained for the reasons of record and those set forth below.

7. Applicant argues that the references cited by the Examiner do not in any way establish lack of enablement of the claimed subject matter. According to Applicant neither the teachings of Branden et al.

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(Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) or Berglund et al. are not representative of the state of the art at the time of filing. With regard to Porteus, Applicant argues that while the reference teaches that refining may be required and that such refining is not trivial, this is not an indication that the zinc finger nucleases are non-functional. Applicant also argues that the claims do not have a “non-toxicity” limitation, thus the assertions made by Porteus et al. about potential ZFN toxicities have no bearing on the instant claims. With regard to *in vivo* methods, Applicant argues that the claims are not directed to gene therapy methods but to specific cells. Applicant submits that the Office has not provided evidence supporting the assertion that methods involving zinc finger fusion proteins only work in isolated cells and as such arguments regarding viability of DNA delivery methods are irrelevant. According to Applicant, the ability of fusion proteins including an engineered zinc finger protein and a functional domain to be expressed and to regulate gene expression *in vivo* is well established. Applicant argues that the teachings of Phillips and Gardlik are irrelevant to the instant case since they do not deal with zinc finger proteins. Regarding Proteus and Urnov, Applicant is of the opinion that these references teach that chimeric nucleases have been successfully used to targeting frequencies of up to 20% in a human disease-causing gene. Applicant submits that the need for further work is not an indication of unpredictability. With regard to the teachings of Urnov et al. regarding potential immunogenicity, Applicant argues that safety is not relevant to the enablement inquiry. Applicant reminds the Office that experimentation is not undue if it is routine.

8. Applicant's arguments have been fully considered and have been found persuasive with regard to the genus of vectors encompassed by claims 21, 99-102, 104. Claims 21, 99-102, 104 are now directed to a genus of vectors which encode chimeric nucleases comprising Zinc finger DNA binding domains. For the reasons indicated above regarding the written description rejection, this rejection as it relates to claims 21, 99-102, 104 is hereby withdrawn. However, Applicant's arguments are not found persuasive with regard to claims 28, 40, 103, 107, 108, which are directed in part to non-isolated mammalian cells. The

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Examiner is well aware that the claims are not directed to gene therapy methods. However references citing the state of the art regarding gene delivery, particularly to humans, and the potential toxicity and limitations of gene targeting for human applications are extremely relevant to the claimed invention in view of the fact that the claims encompass not only isolated cells but cells within a living organism, **including humans**. In fact, the specification discloses that human cells having the recited vectors is the preferred embodiment of the claimed invention because the main intended use of the vectors of the invention is gene targeting (a form of gene therapy) to address many diseases. See, for example, page 1, lines 19-25, page 4, line 9-page 5, line 28, page 38, line 9-page 39, line 2. The specification on page 38, lines 19-20 specifically recites “a preferred cell is a human cell”. The specification is extremely clear as to the main intended use of the vectors and the cells of the invention. Since it is abundantly clear that the scope of the genus of cells claimed includes non-isolated human cells, one of skill in the art would reasonably conclude that the scope of the claims as it relates to non-isolated human cells should also be enabled by the teachings of the specification and/or the prior art.

The Examiner acknowledges that the claims do not recite a “non-toxicity” limitation and agrees that safety by itself is not a criterion of patentability. However, in the instant case, the issues of discriminating between the target of choice and related off-target sites, and potential immunogenicity are not solely issues of safety but rather issues which are directly related to the ability to achieve the desired result, which is to express the desired chimeric nuclease and make the desired repair at the target site. Leaving aside the issue of safety, immunogenicity is important to the issue of enablement since if the presence of the chimeric nuclease results in an immune response to said nuclease, that chimeric nuclease would not be able to act on its target and accomplish the desired repair. Similarly, if the chimeric nuclease is not specific enough to recognize solely its intended target without acting on related off-target sites, such chimeric nuclease could potentially be cytotoxic to the cell and eventually would destroy the cell in which the repair is intended. While applicant argues that the teachings of Porteus (one of the

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inventors of the claimed invention) regarding the additional research that needs to be done to better discriminate between the gene target of choice and related off-target binding sites and how this research is not trivial are not relevant to the issue of enablement, it is noted that contrary to applicant's assertion, the teachings of Porteus et al. are very relevant to the issue of enablement in view of the fact that it is clear from the teachings of Porteus that obtaining a chimeric nuclease which is specific enough to avoid targeting related off-target sites and would not result in cytotoxicity requires a great deal of non-trivial experimentation.

Furthermore, an additional issue regarding the enablement of the claimed cells is the issue of successfully delivering DNAs encoding the chimeric nucleases and donor DNA such that a mammalian cell as claimed can be obtained. The teachings of Phillips and Gardlik regarding the unpredictability of successfully delivering DNA to human tissues and achieving the desired expression are further corroborated by Porteus (one of the inventors of the claimed invention) and Urnov, who, as stated in the previous Office action, point out that one of the challenges of using ZFNs in primary cells is the delivery method (Porteus), and that one the limitations regarding the use of ZFNs in the clinic is the successful delivery of DNAs encoding ZFNs and donor DNA (Urnov). While Applicant argues that the ability of fusion proteins including an engineered zinc finger protein and a functional domain to be expressed and to regulate gene expression *in vivo* is well established, it is noted that in the instant case there is no teaching in the specification or the art supporting the argument that the *in vitro* results found with regard to chimeric nucleases and substrate repair can be found *in vivo*. As previously indicated, Proteus et al. teach that (1) it is unknown whether the techniques that have been used in cultured cell lines (*in vitro*) will work with primary cells or whether other methods such as viral delivery or direct microinjection will work better, and (2) future work will be needed to translate the *in vitro* findings to *in vivo* applications. These statements are in complete agreement with the general consensus in the art regarding the unpredictability of extrapolating *in vitro* results to an *in vivo* environment since the *in vitro* conditions are

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generally well controlled as opposed to the conditions found *in vivo*. Therefore, for the reasons of record as well as those set forth above, one cannot reasonably conclude that the entire scope of the claimed invention is enabled by the teachings of the specification and/or the prior art.

***Claim Rejections - 35 USC § 103***

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 21, 28, 40, 99-104, 107-108 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chouluka et al. (U.S. Publication No. 20020107214, U.S. Application No. 10/917295 filed on 7/27/2001; cited in the IDS) in view of Bibikova et al. (Molecular and Cellular Biology 21(1):289-297, 2001; cited in the IDS) and further in view of Takeuchi et al. (Biochemical and Biophysical Research Communications 293:953-957, 2002). This rejection has been discussed at length in the previous Office action mailed on 5/13/2008. It is maintained for the reasons of record and those set forth below.

11. Applicant argues that Chouluka et al. teach that the nuclease and the repair substrate are carried on separate vectors and that Bibikova et al. teach that linear donor DNA should be introduced separately from the nuclease-encoding vector. Applicant submits that Takeuchi et al. is silent with regard to including both nuclease and repair substrate in one vector. Thus, applicant concludes that the claimed vector would not be obvious over the cited references. With regard to the mammalian cells claimed, Applicant argues that the claims have been amended such that the chromosomal DNA has to be endogenous. Applicant submits that neither Chouluka et al. nor Bibikova et al. teach or suggest cleavage of a chromosomal target. Applicant states that the cell line of Chouluka et al. was modified to include SceI non-endogenous target sites in the chromosome. With regard to Bibikova et al., applicant argues that this reference specifically teaches that the target polynucleotide for the naturally occurring ZFN is microinjected into oocytes. Applicant submits that Bibikova et al. chose not to cleave endogenous

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chromosomal DNA because they were unsure if zinc finger nucleases would result in targeting of endogenous chromosomal DNA by a repair substrate, citing a passage found on page 296, right column, of that reference. Since Takeuchi et al. do not cure the deficiencies of Chouluka et al. or Bibikova et al., Applicant concludes that the claimed invention is non-obvious.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the amendments to the specification and agrees that none of the references specifically teach a single vector comprising the recited nucleic acids. The Examiner also agrees that the working example disclosed by Chouluka et al. shows that the cell used was modified to include a SclI target site. However the Examiner disagrees with Applicant's contention that the claimed invention is not obvious over the cited references. While it may be that in some instances the use of two vectors as opposed to a single one would be advantageous, as indicated in the previous Office action, one of skill in the art would be motivated to use a single vector for the benefit of delivering to the cell all the necessary components for recombination in a single vehicle. While it is agreed that Bibikova et al. teach that one could deliver the chimeric nucleases along with a linear donor DNA molecule carrying the desired alteration (page 296, left column), Bibikova et al. do not teach that only a linear donor DNA molecule could be delivered nor do they teach away from delivering donor DNA as part of the same vector encoding the chimeric nuclease or as circular DNA (e.g., another vector). In fact, Applicant has admitted that Chouluka et al. teach delivering the repair substrate in a separate vector. As such, Chouluka et al. teach that delivering donor DNA is not limited to linear DNA. Clearly, the art does not teach away from delivering donor DNA in other forms beyond linear DNA.

With regard to the "endogenous" limitation now recited in claims directed to a mammalian cell, it is noted that the teachings of Chouluka et al. and Bibikova et al. both teach cleavage of a chromosomal target. The fact that a SclI target site was genetically introduced in the chromosome cell does not change the fact that the target was in the chromosome. It may be that the working examples provided by these

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references do not specifically teach a target which was endogenously present in the host cell used, however it is noted that the introduction of the SclI target site in the chromosome was made to demonstrate that this system can be used to specifically target the chromosome of a host cell for repair. Thus, the “endogenous” limitation is at a minimum suggested by the cited references. Thus, for the reasons of record and those set forth above, the claimed invention is deemed an obvious over the prior art of record.

### ***Conclusion***

13. No claim is in condition for allowance.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez  
Primary Patent Examiner  
Art Unit 1652

DR  
November 15, 2008